
Reviews/Analyses

Ascertainment of risk of serious adverse reactions associated with chemoprophylactic antimalarial drugs

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Serious adverse reactions during malaria chemoprophylaxis are reviewed. Three drugs considered to have caused serious reactions in recent years are pyrimethamine/sulfadoxine (Fansidar), pyrimethamine/dapsone (Maloprim) and amodiaquine. These reactions are principally independent of dose and cannot be determined during screening for optimal doses. However, host factors may precipitate dose-dependent reactions, some of which could be avoided with improvements in drug licensing. Since serious and life-threatening reactions are relatively rare (between 1:1000 and 1:20 000), Phase I to III trials cannot identify them. Reliance must therefore be placed on Phase IV post-marketing studies, including ongoing reviews of national registers, and specially tailored studies to identify the risk using prescription-event monitoring in high-risk populations. Occasionally, medical-record linkage, case-control and cohort studies may provide supportive data. Although large numbers of travellers must, of necessity, be exposed to a drug before relatively rare reactions are identified, the ascertainment of risk using post-marketing surveillance was prevented by the following five deficiencies: lack of awareness of early alerts, inadequate use of national registers, poor attention to epidemiological and statistical rigour, inadequate verification of denominators, and inadequacy of data records. Recommendations are given for minimizing such errors in the future.

Introduction

Because of chloroquine-resistance in *Plasmodium falciparum*, other potentially more toxic drugs were introduced for the prevention and treatment of malaria infections. When resistance to chloroquine was first reported, there was nothing to indicate that the new drugs could be hazardous and guidelines for treatment and prophylaxis were soon changed to include them. When adverse reactions to these new drugs were first published in the early 1980s, malaria specialists were largely unprepared and unable to determine the significance of these alerts. Measurement of the rates of serious drug reactions to

pyrimethamine/sulfadoxine varied widely between 1:5000 to 1:8000 in the USA (1) and 1:150 000 in Switzerland (2), and it was unclear whether these data reflected a true difference or resulted from incompatible study designs and other flaws. WHO therefore called a series of meetings to resolve the conflict arising from ambiguous results, and to propose a rational procedure for formulating malaria prevention guidelines (89). While the differences in rates between countries could not be explained, the meetings promoted greater awareness of the need to quantify risks and benefits associated with malaria and its prevention (3) and it was realized that more refined epidemiological studies were required to determine the risks.*

As a result of all this experience, drugs which may cause serious reactions are now reserved for those at highest risk of severe infection. However, since the degree and intensity of transmission of resistant strains will increase, there will be continued

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interest to explore the effectiveness of potentially toxic drugs (4–6). Furthermore, data generated from studies of risk will be integrated more frequently into modelled analyses (7). We here report the main serious adverse reactions associated with recently used antimalarial drugs, taking into account the scientific criteria and methodological issues that influence risk ascertainment, and suggest how morbidity and mortality associated with the use of potentially toxic chemoprophylactic drugs can be minimized.

Definitions

Adverse drug reactions

An adverse drug reaction is defined as any drug action that is not of diagnostic, therapeutic, or prophylactic benefit to the user.

Seriousness. Reactions associated with chemoprophylactic drugs must be differentiated into non-serious and serious reactions. The former may cause transient impairment and may compromise compliance with chemoprophylaxis. Such reactions, which are particularly associated with proguanil, include nausea and vomiting, mouth ulcers (8–11), and loss of hair (12). They deserve study to help avert poor compliance which may lead to an increased risk of malaria infection. This paper, however, focuses on serious reactions—defined as fatal, life-threatening, disabling or incapacitating. A list of adverse reactions defined as serious by the Committee on Safety of Medicines (in the United Kingdom) has recently been published (13). The chemoprophylactic drugs associated most frequently with serious reactions are pyrimethamine/sulfadoxine, pyrimethamine/dapsone and amodiaquine. Drugs recently employed (mefloquine, doxycycline) have not yet been comprehensively monitored.

Classification

Adverse reactions may be classified according to a number of clinical and biological criteria (14). Reactions are more frequently subdivided as dose-dependent, dose-independent and pseudo-allergic. The majority of serious reactions associated with antimalarial drugs are dose-independent hypersensitivity reactions. Dose-dependent reactions may, however, occur in the following situations:

(i) *Changes in the drug formulation* of either the active ingredient or the excipients.

(ii) *Route of administration*—influencing the uptake and distribution of the drug. Chemoprophylactics are taken orally, and this influence is thus unlikely.

(iii) *Non-compliance* with the recommended dose and regimen may result in over-dosing. At national level, for example, the recommended dose of weekly pyrimethamine/dapsone was doubled without information on the increased toxicity of this dose. Individuals taking an overdose of mefloquine may be at a higher risk because of the long half-life of this drug.

(iv) *Genetic variation* in an individual's ability to metabolize and eliminate drugs; for example, haemolytic reactions associated with G6PD deficiency in quinine, primaquine, and (occasionally) sulfonamide users. The role of slow and fast acetylation, and the relative roles of parent compounds versus their metabolites in relation to adverse reactions requires elucidation.

(v) *Age*—neonates and the elderly are more susceptible to dose-dependent reactions. Dosage is usually adjusted for small children, but often not for those with reduced glomerular filtration rates, as in the elderly. In the United Kingdom, cases over 55 years with agranulocytosis associated with pyrimethamine/dapsone had a significantly higher risk of fatality.^b

(vi) *Pregnancy*—susceptibility of the fetus in the first trimester is well known. Teratogenic reactions have been associated with folate antagonists, like pyrimethamine (15). Sulfonamides increase the risk of neonatal jaundice, haemolysis and kernicterus. Spontaneous abortion, stillbirth, fetal abnormalities, and cleft palate have been attributed to pyrimethamine/dapsone (16). Tetracyclines administered to pregnant and lactating mothers cause dental discoloration in the infant.

(vii) *Drug interactions* may exacerbate toxicity; for example, cimetidine increases the plasma concentration of quinine (17). When taken simultaneously, quinine appears to increase the toxic reactions to mefloquine.^c

(viii) *Concomitant illness*, particularly hepatic and renal impairment, increases the toxicity of drugs. Low glomerular filtration rate (< 10 ml/min) increases the risk of blood dyscrasias and cutaneous reactions to sulfonamides (17). The haematological toxicity of proguanil is increased. Immunocompromised people have increased susceptibility to cutaneous reactions to pyrimethamine/sulfadoxine.

^b See footnote a, page 493.

^c *Central nervous system reactions related to the antimalarial drug mefloquine.* Unpublished WHO document, WHO/MAL/89. 1054, 1989.

Detection of serious adverse drug reactions

Monitoring of reactions

The epidemiological and statistical process of monitoring for drug safety has been comprehensively reviewed (18,19) and, in the context of serious adverse reactions to chemoprophylaxis, is outlined below. Animal models are fallible as predictors of the safety of drugs. Phased human trials with standardized methodologies have thus been adopted in most countries prior to the licensing and marketing of drugs.

Methodological approaches to predict risks post-marketing (Phase IV) are less systematic than the studies conducted during the first three phases.

- Phase I: examining the kinetics and pharmacological properties under closely controlled conditions in healthy volunteers.
- Phase II: prophylactic and therapeutic efficacy and correct dosage established by monitoring the pharmacokinetic properties in a limited number of patients with, or exposed to, the target disease.
- Phase III: evaluation of the efficacy and safety of drugs by clinical trial using up to 100 patients per trial.
- Phase IV: final phase studies to monitor the long-term efficacy and safety of the drug by post-marketing surveillance, including national registers, prescription-event monitoring, and special studies using medical-record linkage and the cohort or case-control approach.

Limitations of Phase I to III studies

The first three phases of drug evaluation can only establish toxicity with rates above 1:100 to 1:300 because of the small sample size (Table 1). To improve this, licensing in most countries is only granted after data on 3000 or more patients are presented from pooled clinical trials. However, rare events of 1:1000 or under still cannot be detected with any precision although mild reactions observed during clinical trials should alert malaria specialists that more serious reactions may occur when drugs are marketed on a larger scale.

Phase IV studies for ascertaining risk

Health policy-makers are therefore dependent on Phase IV studies to establish the risk of less common but serious toxic reactions associated with a drug. Estimates of the risk of serious reactions may be conducted by monitoring the specified drug reaction of all users of the drug. Systematic and ongoing monitoring of drug reactions are most frequently conducted through national registers for adverse reactions, prescription-event monitoring, and medical-record linkage through travellers' clinics.

(1) *Post-marketing surveillance through national registers.* This is dependent on voluntary and spontaneous reporting of adverse reactions to suspect drugs. Reports are received from five main sources; case-report forms (as with the yellow card system in the United Kingdom), pharmaceutical companies, correspondence, death certificates, and medical journals. To establish rates and facilitate risk-benefit judge-

Table 1: The likelihood of observing an adverse drug reaction (ADR) in users^a

	Risk of adverse drug reaction:					
	1/100	1/500	1/1000	1/5000	1/10 000	1/50 000
No. of users for study:						
100	0.63	0.18	0.10	0.02	0.01	0.002
200	0.86	0.33	0.18	0.04	0.02	0.004
500	0.99	0.63	0.39	0.10	0.05	0.01
1000	0.99	0.86	0.63	0.18	0.10	0.02
2000	0.99	0.98	0.86	0.33	0.18	0.04
5000	0.99	0.99	0.99	0.63	0.39	0.10
10 000	0.99	0.99	0.99	0.86	0.63	0.18
No. of users required to observe an ADR: ^b						
95% likelihood	300	1500	3000	15 000	30 000	150 000
97% likelihood	360	1800	3600	18 200	36 400	182 000

^a Adapted, with permission, from Sackett et al. (20).

^b Calculations based on the formula $pr = 1 - e^{-x}$ where pr = probability; e = exponential log; $x = 1/n$ (ADR rate); and $y = n$ exposed.

ments, data on adverse reactions from national registers need to be linked with denominators. Estimates also need to take into account the background incidence (Table 2). Denominators consisting of all users of the drug are seldom available as a direct measure and are often dependent on estimates from sales or prescriptions. Pharmaceutical data, however, often overestimate the number of users because they include overseas sales data and unsold drugs (16). Prescription data may achieve high precision if the estimates are based on random samples of all prescriptions. The use of travel statistics and traveller surveys to estimate the proportion of drug users requires caution because of the biases associated with self-reported use and selected responses. Suggested uses of post-marketing surveillance through national registers are:

- early warning system to detect or confirm trends in incidence;
- generation and review of hypotheses from data;
- review of the spectrum of serious reactions;
- alert for serious but rare adverse reactions;
- establishment of minimum reported reaction rates;
- special investigations of causality after alerts in medical journals (e.g., dose-response relationships); and
- identification of keynote cases which, by inquiry, delineate specific drug-associated syndromes.

Table 2: The minimum number of persons required to be exposed to a drug to detect a specific risk at varying levels of background incidence of adverse drug reactions (ADR)^a

Rate of ADR to be detected	Spontaneous background rate of adverse event	Minimum number to be exposed ^b
1:100	0	360
	1:10 000	520
	1:1000	730
	1:100	2000
1:500	0	1800
	1:10 000	3200
	1:1000	6700
	1:100	35 900
1:1000	0	3600
	1:10 000	7300
	1:1000	20 300
	1:100	136 400
1:5000	0	18 200
	1:10 000	67 400
	1:1000	363 000
	1:100	3 255 000

^a Adapted, with permission, from Mann (18).

^b For a 97% likelihood of observing an ADR.

Surveillance through national registers is inadequate for monitoring of reactions/events with questionable causality (e.g., neurotoxicity leading to trauma) and for early detection of rates.

(2) *Post-marketing surveillance through prescription-event monitoring.* In the United Kingdom, retrospective follow-up of patients prescribed a specified drug may be achieved through prescription-event monitoring (19). Cohorts of patients prescribed a specific drug are followed up retrospectively throughout the country, identifying all events that occurred while taking the drug. This is achieved by requesting information directly from each prescribing doctor, by postal survey. Prescription-event monitoring may be used to identify the spectrum of fairly frequent adverse reactions. This method is inadequate for distinguishing a causal association if the background incidence is high.

(3) Other post-marketing studies are as follows:

(a) *Medical-record linkage.* Records from prescriptions and hospital discharge notes may be linked together to establish the relationship between adverse reactions and drug use. An adaptation to the chemoprophylactic situation is the linkage within travellers' clinics, by linkage with case reports of persons who attended the pre-travel clinic and returned to the same outpatient clinic for treatment of an adverse event. It is thus similar to prescription-event monitoring but without active follow-up of each user. This approach was adopted to identify the high frequency of agranulocytosis with amodiaquine in travellers at a pre-travel clinic in Oxford (21). Computerized systems may provide record linkages at source.

(b) *Case-control.* These studies are used to provide evidence that cases are more likely to have been exposed to the suspect drug than controls. Thus, this type of study may only be used after suspicion of a drug has been raised. Since the type of serious reactions experienced with antimalarial drugs have been such rare natural events, case-control studies have not previously been used to prove the association. However, these studies can play an important role in identifying the influence of important risk factors. Cases may be obtained from reports to national registers and controls from cohort populations, but the representativeness of both populations must be considered. These studies may be used for:

- distinguishing causal association of suspect risk factors, e.g., evaluating whether a previous psychiatric history increases the risk of psychosis with mefloquine; and
- establishing dose-response relationships.

They are inadequate for identification of unsuspected or unmeasured risk factors.

(c) *Longitudinal cohorts.* Longitudinal follow-up of cohorts of travellers using specified antimalarial drugs may establish the frequency of reactions to a suspect drug. Experimental cohorts are most efficient, since many subjects may be allocated to a specific drug regimen. Questionnaire surveys provide another opportunity to collect key data and may be used to identify risk factors. They provide internal denominators for the description of drug use and compliance. Such observational studies are disadvantaged because of the subjects' individual use of drugs and their compliance; larger sample sizes are therefore required before sufficient numbers using a specific regimen are recruited. Both types still achieve greater accuracy in estimating risks in a defined population than a case-control study. These studies may be used for the following:

- early alerts of frequent reactions in travel cohorts;
- exploration of causality;
- occasional alert of a rare reaction (stimulate special inquiry);
- monitoring of rare reactions through international cohorts; and
- determination of absolute as well as relative risks.

They are not suitable for:

- measuring the rates of serious rare reactions in small cohorts; and
- determining the causality and rates if loss to follow-up is high.

Limitations of Phase IV studies

Serious reactions are principally rare disorders and therefore the measurement of risk through any post-marketing system requires time. The timing of wide-spread alerts is of considerable importance because of their influence on premature withdrawal of an efficacious drug, or delayed withdrawal of a severely toxic drug, both actions causing unwarranted morbidity or mortality. The likelihood of detection of an adverse reaction is directly associated with the number of people exposed to that drug. In order to identify a reaction with 95% confidence, a population three times the size of the expected rate must be exposed (Table 1). Thus, with a true reaction rate of 1:5000, at least 15 000 travellers would have to be exposed before we can be 95% confident that one reaction will occur. In practice, however, many thousands of travellers would have to be exposed because initial reactions would not immediately lead malaria specialists to make the association. Alerts of

reactions are usually first raised through correspondence in the literature. These are mostly case reports, and do not provide data for calculating incidence rates (22). There is also a substantial delay of about 69 weeks between the diagnosis and publication of the case (23).

(1) *Limitations of national registries.* Comprehensive national registries provide a unique opportunity to monitor adverse drug reactions. The strengths and weaknesses of the systems, however, must be identified before data are used for policy decisions. Under-reporting and misclassification of causality are the two principal biases associated with all post-marketing surveillance systems. Reporting bias also includes the reporting of inadequate information. Many confounding risk factors need to be collected, including the age of patients, genetic factors, concomitant drug use, presence of other diseases, and drug dose.

(a) *Under-reporting* is the most important bias associated with ascertainment of risk. It occurs when either the patient or doctor fails to recognize or to report. Non-reporting by the doctor may result because of ignorance of the severity of the case or of the necessity to report, fear and guilt of the reaction, or secrecy (for publication). Because of under-reporting, calculations of rates provide the lowest limit of risk using a drug. While up to 90% of reactions to non-steroidal anti-inflammatory drugs were estimated to be missed in the United Kingdom because of reporting bias (18), the reporting of reactions to antimalarials is thought to be considerably higher. Reporting rates of cutaneous reactions to pyrimethamine/sulfadoxine based on national registries in the United Kingdom and Sweden were similar to those achieved during an intense investigation in the USA (1). Reporting may be high because there is increased recognition of adverse reactions in travellers taking monotherapy, compared with elderly and infirm people on multiple therapy. It may also be attributed to the substantial publicity describing cutaneous reactions associated with pyrimethamine/sulfadoxine (1, 24–35). Reporting rates for conditions receiving little publicity may thus be lower; for example, in the United Kingdom six of the nine cutaneous reactions to pyrimethamine/sulfadoxine were published, but none of the three fetal abnormalities (to any drug) and only one of the nine hepatic reactions.^a Reporting is also temporal; ascertainment is low during early post-marketing, when reactions are not attributed to a new drug, and again

^a See footnote a, page 493.

later when associations are well established. This has been witnessed in the United Kingdom where reported reaction rates to pyrimethamine/dapsone (marketed for 16 years) decreased tenfold in the last three years (16).

(b) *Misclassification* makes it necessary for reports to be scrutinized with regard to identified causality. Questions include: were other drugs administered; was the drug really taken; if taken on a previous occasion, was a similar reaction experienced; what occurred after the report; were full details submitted; and has the doctor recently seen similar reactions? Based on this assessment, causality is described as definite, probable, possible, conditional or doubtful (19). Causality is strengthened if the event or reaction:

- was temporally associated with the administration of the suspect drug;
- followed a known response pattern of the suspect drug;
- improved when the suspect drug was removed;
- recurred when the patient was rechallenged with the suspect drug;
- could not be explained by another reason.

Confusion of causality most often occurs either when the event is relatively common (high background incidence) or when other drugs are taken simultaneously, or both. This may cause particular confusion when two antimalarial drugs are taken concomitantly; exaggerated epilepsy and convulsions were recently attributed to chloroquine (36), although they could have been spontaneous reactions unrelated to the drug (37). In the national register they were attributed to compound antimalarials taken concomitantly.^a Misclassification may also occur in the context of seriousness. The clinical decision of seriousness, although made by experts, is still a value judgement and is difficult to quantify. Data from the United Kingdom, however, suggest that the criteria used are rigorous, since between 10% and 20% of all reactions defined as serious proved to be fatal (16).

(2) *Limitations of other approaches.* These are described below.

(a) *Prescription-event monitoring and medical-record linkage.* This is performed retrospectively and data-gathering takes time. It is dependent on physicians' responses, which in the United Kingdom are currently about 60% (19). The expenses also prohibit national prescription-event monitoring for

the commonly used chemoprophylactic drugs. Drugs prescribed on private prescriptions are less accessible for follow-up.

(b) *Case-control* is limited to suspected associations. The case-control method can only establish relative risks. As such it can never prove causal associations but can provide strong evidence. Since data for case-control studies normally originate from spontaneous reporting systems, they are influenced by the same biases (see above). This would include inadequate or incomplete data recorded in reports and would particularly limit analyses that attempt to demonstrate a relationship between dose, duration of use, and severity of the event.

(c) *Cohort.* The rarity of serious reactions limits the usefulness of prospective cohorts. As previously discussed, a population three times the expected rate must be examined, making this a very time-consuming and expensive approach for risk ascertainment. Monitoring of an observational cohort is further handicapped because only a non-randomized proportion of the population sampled will have taken the suspect drug. Moreover, self-reported information cannot be verified on all occasions.

Current experience

Published case reports and data generated from post-marketing surveillance systems have been reviewed to assess the types and frequency, and the efficacy of adverse drug reaction monitoring. Case reports have been frequently published and cannot all be cited in this article. Rates have only been measured by a few countries; comparative assessment will thus be limited to data reported from the USA (1, 38), Sweden (39, 40), Switzerland (2) and the United Kingdom (16, 21). Relatively frequent reports of non-serious reactions to antimalarial drugs have been made by travellers during observational cohort studies (10, 41, 42), with an incidence ranging between 12% and 40%. Data from these studies will not be reviewed.

Principal serious reactions during chemoprophylaxis

(a) *Pyrimethamine/sulfadoxine.* Cutaneous reactions are the most serious reactions with pyrimethamine/sulfadoxine. The case-fatality rate was 50% in the United Kingdom (16), 29% in the USA (1), and 29% in Sweden (37). Other serious reactions published in case reports are hepatitis (43–45) and pulmonary lesions (46, 47). A review of all cases reported to the British and Swedish national register revealed a wider range of reactions including also blood cell dyscrasias, eye disorders, abortion and convulsions.

^a See footnote a, page 493.

(b) *Pyrimethamine/dapsone*. The principal reactions associated with pyrimethamine/dapsone are white blood cell dyscrasias (48–52). The reactions in Sweden occurred with twice weekly doses; three of the eight cases (38%) were fatal (40). The fatality rate in British travellers with agranulocytosis, who took either one or two tablets weekly, was 27%. Four of the five deaths were in patients over 50 years of age. Case reports of serious cutaneous reactions (53, 54) and pulmonary disorders (55) reported in the United Kingdom were all associated with pyrimethamine/dapsone taken at once weekly doses. A variety of other serious reactions were identified in a review of cases reported to the British national register—such as hepatitis, fetal abnormalities, and convulsions.

(c) *Amodiaquine*. In the United Kingdom, 84% of serious reactions reported to be associated with amodiaquine were white blood cell dyscrasias, with a case fatality rate of 12% (16). Reports of agranulocytosis have also been frequently publicized in Europe (56–60). The incidence of hepatic toxicity appears to have been higher in continental Europe (61–63); in the United Kingdom, only two of the 19 cases had hepatic reactions.

Rapidity of onset of serious reactions during chemoprophylaxis

Chemoprophylactic antimalarial drugs predominantly cause dose-independent idiosyncratic and hypersensitivity reactions. They cannot therefore be predicted by screening for the optimal dose. Serious cutaneous reactions appear within the first few doses taken. In the United Kingdom and Sweden all cutaneous reactions associated with pyrimethamine/sulfadoxine occurred within a mean of two weeks and a maximum of four weeks (16, 40). In the United Kingdom, all four fatalities had continued to take tablets after the onset of symptoms, compared with only one of the four survivors. Longer periods of up to seven weeks' dosing were reported in the USA (1). Cutaneous reactions associated with pyrimethamine/dapsone in British users also occurred within three weeks (16). Other reactions experienced at the beginning of prophylaxis were cyanosis, convulsions, and respiratory disorders. In the United Kingdom, symptoms associated with agranulocytosis and hepatic disorders were experienced after more prolonged prophylaxis, ranging from 5 to 14 weeks and 4 to 8 weeks, respectively (16).

How rates were measured

(a) *Pyrimethamine/sulfadoxine*. A cluster of cases with serious cutaneous reactions in the USA initiated a retrospective study (1). A brief review of national

registers and pharmaceutical and travel survey data in Switzerland revealed very different risks (Table 3) (2); Swiss specialists postulated that rates were higher in the USA because of the synergistic properties of chloroquine. Data reviewed from the national register in the United Kingdom appeared to support this (33); however, the proportion of chloroquine users had been overestimated because of duplicates.* Data from Sweden indicated that reactions to pyrimethamine/sulfadoxine alone were within the same magnitude as the U.S. figures (39). Data from the United Kingdom were used to explore why rates differed between countries.* A comparison between multiple denominators showed that pharmaceutical sales data were fourfold higher than prescription data, and that their use subsequently reduced the mean rates fourfold. Overestimation occurred because the pharmaceutical data included sales to multinationals who distributed the tablets to their staff overseas, and unsold drugs in pharmacies. This feature of the sales probably had a substantial bearing on the estimates of denominators in Switzerland.

(b) *Pyrimethamine/dapsone*. Hospitalized travellers with agranulocytosis due to no accountable etiology alerted infectious disease specialists in Sweden to the potential toxicity of pyrimethamine/dapsone taken twice weekly. An international review of all cases suggested that pyrimethamine/dapsone had a lower toxicity when taken as a single dose (64). A recent review of cases in the United Kingdom suggested that this may be true, but data were not available to measure the dose-response (Table 3) (16).

(c) *Amodiaquine*. A cluster of cases with neutropenia, identified through a travellers' clinic in the United Kingdom, initiated an investigation on the potential toxicity of amodiaquine (Table 3) (21). No comparative data were available from the USA or Sweden as the drug had not been marketed there.

Major errors associated with ascertaining risk

Judgement on toxicity relies heavily on data generated through post-marketing surveillance systems because clinical trials cannot identify rare but serious reactions. The quality of data generated through these systems therefore requires careful inquiry. Five key problems associated with the ascertainment of risk in recent years have been identified and are described below.

(1) Lack of awareness of first alerts

(a) *Pyrimethamine/sulfadoxine*. Evidence of the toxicity of sulfadoxine was published as early as 1968 (65) and six case reports described the seriousness of

* See footnote a, page 493.

Table 3: Rates of serious adverse reactions to chemoprophylactic drugs

	USA	Switzerland	Sweden	United Kingdom
Pyrimethamine/sulphadoxine:				
All cutaneous reactions	1:5000–1:8000	1:150 000	1:10 200	1:4900
Fatal cutaneous reactions	1:11 000–1:25 000	x ^a	1:37 000	1:11 100
Hepatic disorders	1:16 000–1:54 000	x	1:4500	1:11 100
All serious reactions	x ^a	x	1:1900	1:2100
All fatal reactions	x	x	1:33 000	1:11 100
Pyrimethamine/dapsone:^b				
White blood cell (WBC) dyscrasias	x	x	1:2000	1:20 000
Fatalities from WBC dyscrasias	x	x	1:5300	1:60 200
All serious reactions	x	x	1:900	1:9100
All fatal reactions	x	x	1:5300	1:75 200
Amodiaquine:				
White blood cell dyscrasias	x	x	x	1:2200
Fatalities from WBC dyscrasias	x	x	x	1:31 300
All serious reactions	x	x	x	1:1700
All fatal reactions	x	x	x	1:15 650

^a x = no data available.

^b In Sweden two tablets. In the United Kingdom one tablet was recommended for 13 of the 16 years that Maloprim has been available; two tablets were recommended by some (not all) authorities between 1980 and 1983.

cutaneous reactions to pyrimethamine/sulfadoxine in 1982 and 1983, but failed to rouse immediate international concern.

(b) *Pyrimethamine/dapsone*. Sixteen cases of agranulocytosis with eight deaths occurred in 200 000 servicemen taking dapsone in Viet Nam in the early 1970s, giving a rate of 1:12 500 (66). The incidence was disputed because of the lack of evidence of reactions in leprosy patients (67, 68) although early reports were evident in the literature (69–71). In recent years, both agranulocytosis and cutaneous reactions have been further reported in leprosy patients (72–76).

(c) *Amodiaquine*. Between 1950 and 1983, 20 cases of agranulocytosis associated with amodiaquine were published in the literature (77–86). It is unclear whether these were known but rejected because only 15% had been prescribed amodiaquine for malaria prophylaxis, or whether a historical review had not been performed prior to marketing.

(2) *Inadequate application of national registers*

Reports collated by national registers have not been systematically reviewed after new drugs are first marketed. It is only the clustering of cases at clinics or hospitals that, either by vigilance or serendipity, alerted specialists of the need to assess risks using national registers. Subsequently, reaction rates of 1:2000 have taken about two to three years to establish, rates of 1:5000 have taken between five and six years, and rates of 1:10 000 or lower have taken

many years to determine.¹ It can be assumed that these lag times could be reduced if reports recorded in national registers were routinely investigated by specialists, with appropriate computer support, as part of an ongoing process of post-marketing surveillance of new antimalarials.

(3) *Inadequate attention to epidemiological and statistical rigour*

Inappropriate epidemiological and statistical methods have led to faulty results. International monitoring of adverse reactions, and comparative studies between countries were not performed. Had this occurred, false associations with chloroquine, and extremes in rates, could have been avoided. Few studies have attempted to measure the precision of their analyses. The rarity of adverse reactions, compounded by sampling errors (both denominators and numerators), inevitably causes substantial variance. Biases associated with the method and calculation of confidence limits are not generally presented.

(4) *Inadequate verification of denominators*

Greater caution is needed when linking case data with denominators. Travel statistics and select surveys of travellers do not provide sufficient data to estimate the denominators, but may be used to support calculations based on prescriptions. Caution is also required when interpreting denominator data derived from pharmaceutical sales. Rates based on these data should be considered to be minimum estimates.

(5) *Inadequate data recorded or analysed*

Data required to confirm causality and dose-

¹ See footnote a, page 493.

response relationships have not always been adequately recorded through national registers. Inadequate follow-up of serious reactions is of importance, and may be due to lack of resources. Data used to strengthen causal hypotheses are not routinely collected; for example, the time of onset following administration, the dose and regimen of the drug, and the improvement or deterioration of the individual during removal or rechallenge with the suspect drug. Furthermore, dates of the reaction are seldom provided in published reports or through the register, and thus cannot alert prescribers to the possibility of batch impurities. Age, while postulated as a risk factor (87, 88), is seldom included within the analyses.

Recommendations

It is in the best interest of consumers, physicians and pharmaceutical companies that the risks associated with prophylactic drugs should be adequately monitored. Serendipity has played a major role in identifying risks associated with chemoprophylactic drugs and a more systematic approach is clearly required. Implementation of the following recommendations may contribute towards the development of a more comprehensive system to minimize the potential hazards of antimalarial drugs.

Prelicensing management of new drugs or higher doses

(1) Investigate safety/efficacy and recommend limitations:

- review historical literature, including safety record when used for alternative diseases, and reactions to related compounds;
- review Phase I to III trials and post-marketing data, where available; and
- explore biological markers that identify susceptible users.

(2) Advise pharmaceutical companies on marketing information needed:

- clinical indications for use of the drug; and
- information required for package insert and literature for physicians.

Licensing management

(3) Ensure that:

- all reviewed data are brought forward for licensing policy;
- the package insert adequately warns patients about drug safety and contraindications;
- special literature fully assists prescribing physicians;

- a post-marketing system covers the possible spectrum of adverse reactions; and
- the drug will be targeted appropriately (if safety is unclear, limit the distribution).

Postlicensing management

(4) Extend standardized methods of monitoring in order to:

- routinely follow up high-risk cohorts using the new drug;
- advise physicians to report to the national register/malaria unit;
- encourage publication of all types of reactions; and
- classify all antimalarials as prescription drugs.

(5) Enhance data collected through national registers in order to:

- standardize and improve routine data collected in each country;
- assess and encourage national reporting rates;
- encourage the use of national data for reviews and studies; and
- provide open access to case data (without revealing names) for investigations by experts.

(6) Encourage systematic national reviews of guidelines using:

- reviews of data from national registers;
- national reports linked with denominators, preferably prescription data; and
- reaction rates in conjunction with efficacy data to evaluate the risks and benefits of antimalarial drugs.

(7) Establish a centralized international collaborative unit to:

- develop standardized methods to collect and analyse data;
- encourage the use of appropriate epidemiology and statistics;
- advise pharmaceutical companies on appropriate research, distribution of information, and funding;
- stimulate international collaboration and shared data systems; and
- conduct in-depth global inquiries into the risks of adverse reactions, including their ascertainment and management.

(8) Develop the travellers' clinics as ongoing monitoring units to:

- routinely gather standardized data on all attenders;
- gather comprehensive data on denominators;

- carry out special cohort studies of high-risk groups and clinical validation of self-reported data; and
- collect quantifiable data, including blood samples and degree of seriousness of adverse reactions.

Acknowledgements

We are most grateful to the Adverse Drug Reaction Advisory Committee in Sweden and the Medicines Control Agency/Committee on Safety of Medicines in the United Kingdom for facilitating access to their national registers. Dr Anders Bjorkman was supported by the Swedish Medical Research Council. Dr Penny Phillips-Howard received funds from the Malaria Action Programme of WHO and from British Airways. Dr R. Mann and Dr L. Molineaux kindly reviewed the manuscript.

Résumé

Chimio prophylaxie du paludisme: Evaluation des risques d'effets indésirables graves

A la suite de l'apparition du paludisme à *Plasmodium falciparum* chloroquinorésistant, il a fallu employer des médicaments potentiellement plus toxiques pour prévenir et traiter la maladie. Effectivement, au début des années 80, plusieurs cas de réactions toxiques graves à trois des principaux médicaments utilisés pour la prophylaxie du paludisme ont été signalés spontanément. Des réactions cutanées sévères ont été observées avec l'association pyriméthamine/sulfadoxine, bien que le risque fût nettement différent suivant les pays; d'autre part des dyscrasies leucocytaires ont été attribuées à l'association pyriméthamine/dapsone et à l'amodiaquine. Ces complications se caractérisaient par un taux de létalité élevé, compris entre 12% et 50%. Des cas de toxicité hépatique ont également été signalés pour ces trois médicaments, mais avec un taux de létalité beaucoup plus faible. Les réactions cutanées sont généralement survenues au cours des deux à trois premières semaines, tandis que l'agranulocytose et les troubles hépatiques ont été observés plus tardivement, soit après un traitement prophylactique de quatre à quatorze semaines.

La plupart des pays ont déjà adopté des protocoles normalisés comportant trois phases pour les essais cliniques qui doivent être effectués préalablement à l'autorisation de mise sur le marché et à la commercialisation d'un médicament. Toutefois, ces trois phases ne peuvent révéler une éventuelle toxicité que si le taux d'effets indésirables dépasse 1:100 à 1:300. Pour formuler des

recommandations en matière de politique sanitaire, il faut donc disposer d'études après commercialisation (pharmacovigilance) de phase IV, seules capables d'évaluer les risques de réactions graves moins fréquentes. Ces études peuvent consister en un examen permanent des registres nationaux, de façon à établir un rapport entre les réactions indésirables signalées et un dénominateur qui peut être le nombre d'utilisateurs du médicament incriminé; on peut aussi entreprendre des études spéciales, telles que la surveillance des prescriptions (*prescription-event monitoring* ou PEM) dans les populations à haut risque, et le raccordement des dossiers médicaux dans les dispensaires pour voyageurs. Parfois, des études cas-témoins peuvent mettre en évidence un important facteur de risque et des enquêtes longitudinales portant sur des cohortes de voyageurs permettent d'estimer la fréquence des réactions les plus courantes à un médicament, tout en identifiant les facteurs de risque.

La pharmacovigilance présente des limites du fait que tous les cas ne figurent pas dans les registres nationaux et que des erreurs sont commises dans la classification des liens de causalité et de la gravité des réactions. La surveillance des prescriptions demande beaucoup de temps et les études cas-témoins sont limitées à l'étude de réactions ou de facteurs de risque déjà soupçonnés; quant aux études de cohortes, pour des raisons logistiques, elles ne permettent de quantifier que les effets secondaires les plus fréquents. S'il est évident qu'un grand nombre d'individus doivent être exposés à un médicament avant qu'une réaction relativement rare soit identifiée, il n'en est pas moins vrai que ces dernières années, la pharmacovigilance aurait dû permettre d'évaluer le risque plus rapidement. Cinq erreurs capitales sont responsables de ce retard: le peu d'attention accordé aux premières observations, le mauvais usage des registres nationaux, le manque de rigueur épidémiologique et statistique, une vérification insuffisante des dénominateurs et la mauvaise qualité des données enregistrées, notamment en ce qui concerne les liens de causalité et les facteurs de risque, tels que la dose de médicament et l'âge des patients. Des recommandations ont donc été proposées pour corriger autant que possible cette situation. En ce qui concerne l'autorisation de mise sur le marché et les étapes préalables à celle-ci, il a notamment été recommandé de procéder à des études sur l'innocuité et l'efficacité des médicaments, de recommander des limites d'utilisation et de mieux définir les populations cibles. Quant aux mesures préconisées après la mise sur le marché, elles

consistent à développer les méthodes normalisées de surveillance, à améliorer la collecte des données grâce aux registres nationaux, à encourager les enquêtes nationales systématiques et à mettre en place des unités de surveillance dans les dispensaires pour voyageurs. Enfin, une unité centralisée de recherche internationale devrait être créée pour stimuler et coordonner la collecte et l'évaluation de ces données.

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